



Plasma leptin in obesity related hypertension

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Abstract

Background and Purpose: It is well known that obesity is related to hypertension through several mechanisms, such as sympathetic overactivity and excess renal sodium reabsorption. Obesity and hypertension may also be linked by leptin, a peptide that is elevated in obese individuals. Leptin is an adipocyte derived hormone that acts in hypothalamus to regulate appetite, energy expenditure and sympathetic nervous system outflow, as well as in peripheral tissues, such as blood vessels and kidneys. The aim of our research was to determine plasma leptin in hypertensive and normotensive obese patients with the same body mass index (BMI) and show a possible difference between leptin levels in these two groups of patients.

Materials and Methods: The research was carried out on 21 hypertensive and 19 normotensive patients (20 men and 20 women) with BMI in range 30–35 kg/m², normal values of fasting plasma glucose, urea and creatinine. Leptin was determined using Elisa method.

Results and Conclusion: The results showed that men had significantly higher waist to hip ratio (W/H). Plasma leptin was significantly higher in hypertensive women as well as in hypertensive men ($p=0.03$) in relation to normotensive patients. There was also significant difference in serum creatinine and creatinine clearance between normotensive and hypertensive women, although creatinine was within normal range. There was a significant difference in serum triglycerides between men and women in general, where men had higher values ($p=0.016$). This confirmed that leptin correlates with hypertension in both men and women.

INTRODUCTION

Hypertension and obesity are common risk factors for the development of cardiovascular diseases, along with diabetes and hyperlipidemia. The prevalence of hypertension in developed countries in Europe is about 44%, while in North America it is about 28% (1). Almost a half of hypertensive patients are obese. The prevalence of hypertension in obese individuals is two times higher than in general population. Therefore, many studies have been focused on explaining the connection between obesity and hypertension. Adipose tissue is the key organ for production of cytokines that are possible mediators of obesity related hypertension (2). One of the cytokines – adipokines that might have an important role in the pathophysiology of obesity induced hypertension is leptin. It is a 16 kDa protein secreted by adipose tissue (3) which acts in hypothalamus to regulate food intake and energy expen-

diture. It is also involved in a number of physiological processes such as regulation of carbohydrate and lipid metabolism, gastrointestinal and cardiovascular function, inflammatory processes, immune function and reproduction (4). Plasma leptin concentration is proportional to the amount of white adipose tissue and it is increased in obese individuals (5). Leptin levels are higher in women than in men. Leptin is secreted in a circadian rhythm where morning levels are relatively high in lean people, the lowest value is obtained at noon and peak values are obtained in the evening. The evening values are related to numerous factors like hormones, circadian rhythm and dynamics of food intake (6).

It is well known that obesity is related to hypertension as both are factors of metabolic syndrome. Obesity induced hypertension is related to sympathetic overactivity as well as to excess sodium reabsorption. Leptin is a possible mediator of obesity-related hypertension since it acts in the hypothalamus by stimulating sympathetic nervous system (SNS) centrally, which indirectly causes vasoconstriction and excess renal sodium absorption (7). Thus, leptin centrally increases blood pressure and heart rate (8). Through its systemic actions leptin affects blood vessels stimulating nitric oxide (NO) production which leads to vasodilation (9). In the kidney, leptin affects renal tubules to promote natriuresis and diuresis (10). Some studies have shown that acute administration of leptin has no effects on blood pressure unless leptin is administered directly into the central nervous system (CNS) (11). Then, only leptin-induced sympathoactivation takes place and systemic actions of leptin such as NO production and natriuresis are not induced. However, chronic administration of leptin leads to a rise in blood pressure (12). Therefore, obesity could be considered a state of chronic hyperleptinemia with the consequences similar to those in chronic leptin infusion. Several studies have shown a positive correlation between leptin and hypertension (13, 14) but the study on Japanese-Brazilian women suggested that leptin is not independently related to hypertension in women (15). The aim of our study was to determine plasma leptin level in hypertensive and normotensive obese patients and show a possible difference between leptin levels in both groups of patients, i.e. men and women, using ELISA method.

PATIENTS AND METHODS

The study included twenty-one hypertensive and nineteen normotensive patients (20 male and 20 female). The signed informed consent was obtained from all subjects. The study included patients with BMI in 30–35 kg/m² the range. All patients led sedentary lifestyle. Exclusion criteria were elevated serum creatinine and impaired glucose metabolism. Hypertensive patients were taking antihypertensive medications and twenty patients were taking lipid lowering medications.

Patients were divided into four groups according to sex and the presence of hypertension. Hypertension was defined as blood pressure values of 140/90 mmHg or

above measured at least three times separately or as taking antihypertensive therapy for at least 1 year prior to the study.

Anthropometric measurements

Weight and height were measured by standard methods. Waist circumference was measured at the umbilical level, in the middle between the lowest rib and the iliac crest. Hip circumference was measured at the trochanter level. BMI was calculated to confirm the inclusion criterion. Waist to hip ratio (WHR) was calculated as it is the most useful parameter of obesity and the simplest anthropometric parameter for predicting a wide range of risk factors and related health conditions.

Biochemical analysis

Glucose, creatinine, cholesterol, triglycerides, low density lipoproteins and high density lipoproteins were determined in serum by standard methods. Patients fasted for at least 12 hours prior to the procedure. Creatinine clearance was calculated using Cockcroft-Gault equation – $GFR = (140 - \text{age}) \times (\text{weight in kilograms}) \times (0.85 \text{ if female}) / (72 \times \text{creatinine})$.

Leptin determination

Blood samples were taken from all patients between 7 and 7:30 am after the 12 hour fasting period. Plasma leptin was measured in the meantime using ELISA method (Leptin ELISA, IBL, Hamburg, Germany). Standard values for non-obese persons (BMI 18–25 kg/m²) were 2.05–5.63 ng/mL for men and 3.63–11.09 ng/mL for women.

Statistical methods

Data are presented as mean \pm SD. All statistical tests were two-sided and carried out to a significance level (p) of 0.05. Shapiro-Wilks test of normality was used to analyse leptin distribution in all patient groups. According to the results of Shapiro-Wilks test, the obtained values are equally distributed, therefore we used Student t -test when checking the statistical significance of the difference in average leptin values in all groups of patients. Data were prepared for analysis in Microsoft Excel 2003. Statistical analysis was made by SPSS 15.0 for Windows Evaluation Version and Statistica 7.1.

RESULTS

Anthropometric and biochemical data are presented in Table 1. Waist to hip ratio was significantly higher in men than in women ($p < 0.005$). Plasma leptin levels were significantly higher in hypertensive obese patients than in normotensive obese patients in both genders, ($p = 0.031$ in women, $p = 0.031$ in men) (Figure 1, 2). The results also showed statistically significant difference in creatinine and creatinine clearance between normotensive and hypertensive women ($p = 0.04$ and $p < 0.001$, respectively), but both parameters were within normal range. There was no significant difference in triglyceride

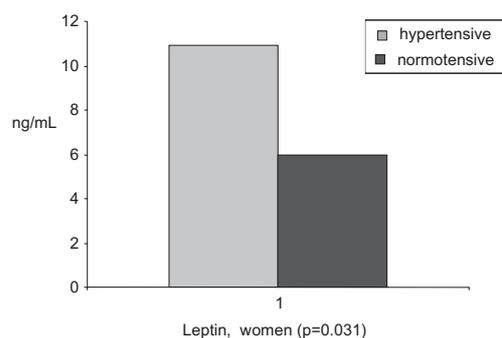


Figure 1. Leptin in hypertensive women is significantly higher than leptin in normotensive women.

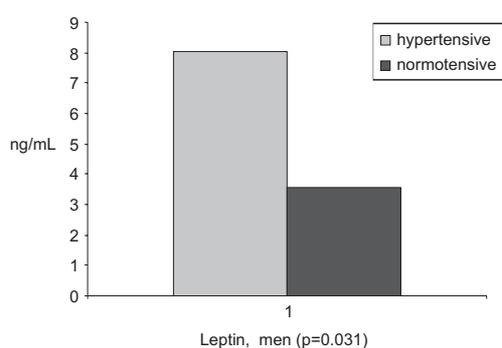


Figure 2. Leptin in hypertensive men is significantly higher than leptin in normotensive men.

and cholesterol levels in NT and HT subjects regardless of gender, but triglycerides were significantly higher in men than in women ($p=0.016$).

DISCUSSION

The aim of this study was to determine whether there is significant difference between plasma leptin levels in

hypertensive and normotensive patients with the same BMI. The results from earlier studies showed strong correlation between leptin and hypertension in humans suggesting that leptin has a significant role in the pathophysiology of obesity induced hypertension, but some studies were not able to confirm this association (15). As previous studies revealed that increased leptin levels combined with decreased NO production and enhanced sympathetic activity may contribute to blood pressure elevation in the obese (14), this study aimed to verify this finding once again. Leptin has no effect on blood pressure in healthy eutrophic subjects because it has pressor and depressor effects that are in constant balance in healthy individuals (16). Our results indicate that the balance between those pressor and depressor mechanisms is damaged. The possible explanation is selective leptin resistance (17) where only pressor effects take place and depressor effects of leptin are lost. The mechanism of selective leptin resistance has still not been identified, but theories involve intracellular signalling disruption and saturable transport across blood-brain barrier (18). Due to selective leptin resistance, the preserved sympathoactivation causes pressor effects in the kidneys and blood vessels, thus elevating blood pressure and leading to further cardiovascular complications.

It should be noted that hypertensive patients in our study were treated with antihypertensive medications. Previous studies suggested that antihypertensive agents have metabolic effects beside blood pressure lowering such as increasing level of adiponectin and decreasing leptin. Therefore, the difference between plasma leptin levels in hypertensive and normotensive patients might have been greater if there was no influence of antihypertensive medication (19). Also, the difference between leptin levels in men and women was not as great as expected, which may be explained by higher WHR in men. WHR >1 predicts abdominal adiposity but it is still un-

TABLE 1
Anthropometric and biochemical data.

	Hypertensive men	Normotensive men		Hypertensive women	Normotensive women	
No	10	10		11	9	
age (years)	57.1±8.35	46.8±12.5		62.45±9.77	43.55±8.81	
w/h	1.02±0.02	0.99±0.07		0.89±0.04	0.85±0.07	
BMI (kg/m ²)	32.05±1.16	31.8±1.36		33.06±1.84	33.22±1.83	
cr (µmol/L)	89.8±14.4	89.1±11.56		72.9±13.3	61.55±8.01	
crc (mL/s)	1.9±0.39	2.23±0.56		1.64±0.32	2.41±0.4	
gl (mmol/L)	5.61±0.52	5.34±0.46		5.41±0.93	4.96±0.51	
ch (mmol/L)	5.84±1.08	5.93±0.87		5.56±0.98	5.64±1.19	
tg (mmol/L)	2.62±1.88	2.67±1.43		1.47±0.6	1.75±0.84	
leptin (ng/mL)	8.022±5.33	3.57±2.74	p=0.031	10.92±4.87	5.93±4.61	p=0.031

Mean ± SD, unless otherwise stated
w/h – waist to hip ratio, BMI – body mass index, cr – creatinine, crc – creatinine clearance, gl – glucose, ch – cholesterol, tg – triglycerides

certain whether leptin correlates better with abdominal or peripheral adiposity.

It is known that ACE inhibitors reduce glomerular filtration by 20 %, which may explain the fact that serum creatinine was higher while creatinine clearance was lower in hypertensive women. There was no significant difference in men. The reason might be the small number of patients included in the study, which is actually its major drawback.

The obtained results confirmed the correlation between plasma leptin level and hypertension. Mechanisms for development of selective leptin resistance seem to be the main leading cause for the development of obesity related hypertension, and they need to be a subject of further research.

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